EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory Considerations for Product Approval

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Disclaimer

"I attend this conference as an individual expert, and do not represent the CAT.

The views expressed here are my personal views, and may not be understood or quoted as being made on behalf of the CAT or reflecting the position of the CAT".

Legal status of the Advanced Therapy Medicinal Products (ATMP)

Regulation 1394/2007/EC

This Regulation is a *lex specialis , which introduces additional provisions to those laid down in Directive 2001/83/EC.*

The scope of this Regulation should be to regulate advanced therapy medicinal products which are intended to be placed on the market in Member States and either prepared industrially or manufactured by a method involving an industrial process, in accordance with the general scope of the Community pharmaceutical legislation laid down in Title II of Directive 2001/83/EC.

Legal status II

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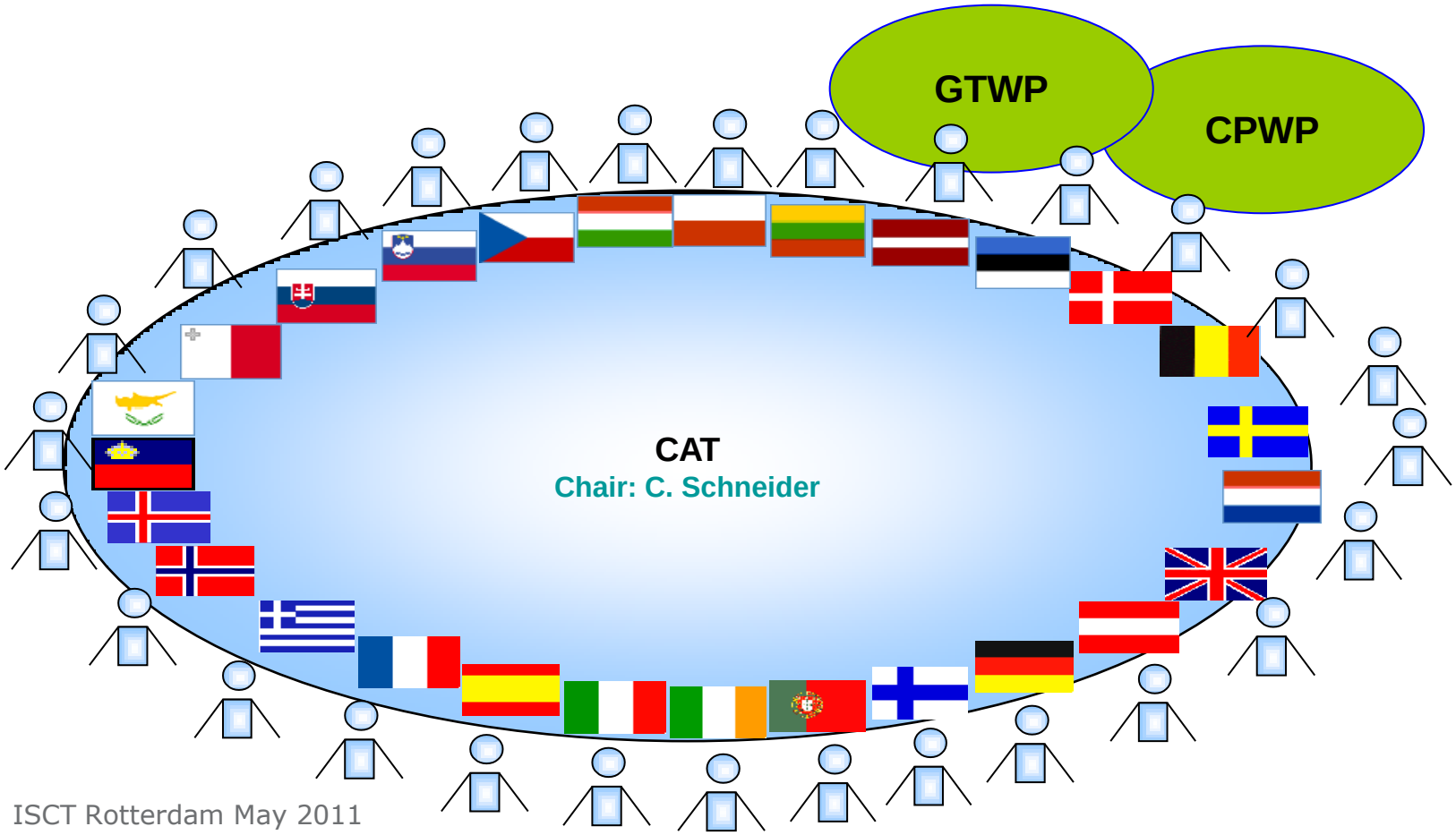
- ***intended to be placed on the market in Member States and***
- ***either prepared industrially or manufactured by a method involving an industrial process,***

in accordance with the general scope of the Community pharmaceutical legislation laid down in Title II of Directive 2001/83/EC.

To foster scientific excellence in the evaluation and supervision of medicines, for the benefit of public and animal health

- Network of European experts (+3500)
- 6 Scientific Committees (CHMP, CAT, COMP, PDCO, CVMP, HMPC & …)
- Over 15 working parties (human unit)
- CP (for ATMPs): 1 single market
- Motto: Science, Medicines, Health
- Values: Europe, public health, innovation, sense of purpose, quality, transparency, integrity, honesty, objectivity, impartiality (CoI)

European Structure
A dedicated committee at EMA



Legislation

Regulation EC (No) 1394/2007

Medical Devices 93/42/EEC

Medicinal Products 2001/83/EC

Advanced Therapies

Science

Medical Devices | Tissue Engineering | Cell Therapy | Gene Therapy | Biotech (e.g. insulin) | Pharmaceuticals (e.g. aspirin)

Committee for Advanced Therapies (CAT) expertise

CHMP expertise

ATMP's definition according to Regulation 1394/2007/EC

the following definitions shall apply for the purposes of this Regulation:

(a) 'Advanced therapy medicinal product' means any of the following medicinal products for human use:

— a gene therapy medicinal product as defined in Part of Annex I t o Directive 2001/83/EC,

— a somatic cell therapy medicinal product as defined Part IV of Annex I t o Directive 2001/83/EC,

— a tissue engineered product as defined in point (b).

2.1. **Gene therapy medicinal product**

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

(a) it contains an active substance which contains or consists of a **recombinant nucleic acid** used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

(b) its therapeutic, prophylactic or diagnostic **effect relates directly** to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

2.2. **Somatic cell therapy medicinal product**

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

contains or consists of cells or tissues that have been subject to **substantial manipulation** so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered,

or of cells or tissues that are **not intended to be used for the same essential function(s)** in the recipient and the donor; EN L 242/4 Official Journal of the European Union 15.9.2009

and is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

(b) Tissue engineered product

means a product that:

— contains or consists of engineered cells or tissues, and

— is presented as having properties for, or is used in or administered to human beings with a view to **regenerating, repairing or replacing** a human tissue.

(c) Cells or tissues shall be considered 'engineered'

if they fulfill at least one of the following conditions:

— the cells or tissues have been subject to **substantial manipulation**, so that biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved. The manipulations listed in Annex I, in particular, shall not be considered as substantial manipulations,

— the cells or tissues are not intended to be used for the same essential function or functions in the recipient as in the donor.

Transplant procedures are regulated by National Competent Authorities

Directive 2004/23/EC

on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells

and the "daughters" Directive 2006/17/EC and Directive 2006/86/EC

The procurement of tissue and cells as raw materials for the production of Cell based Advanced Therapy Medicinal Product are regulated according the prescription of these Directives. The traceability has to be harmonized.

Centralized Procedures pertaining to CAT

- MAA
- Classification
- Certification

(It contributes to the specific Scientific Advice done by SAWP)

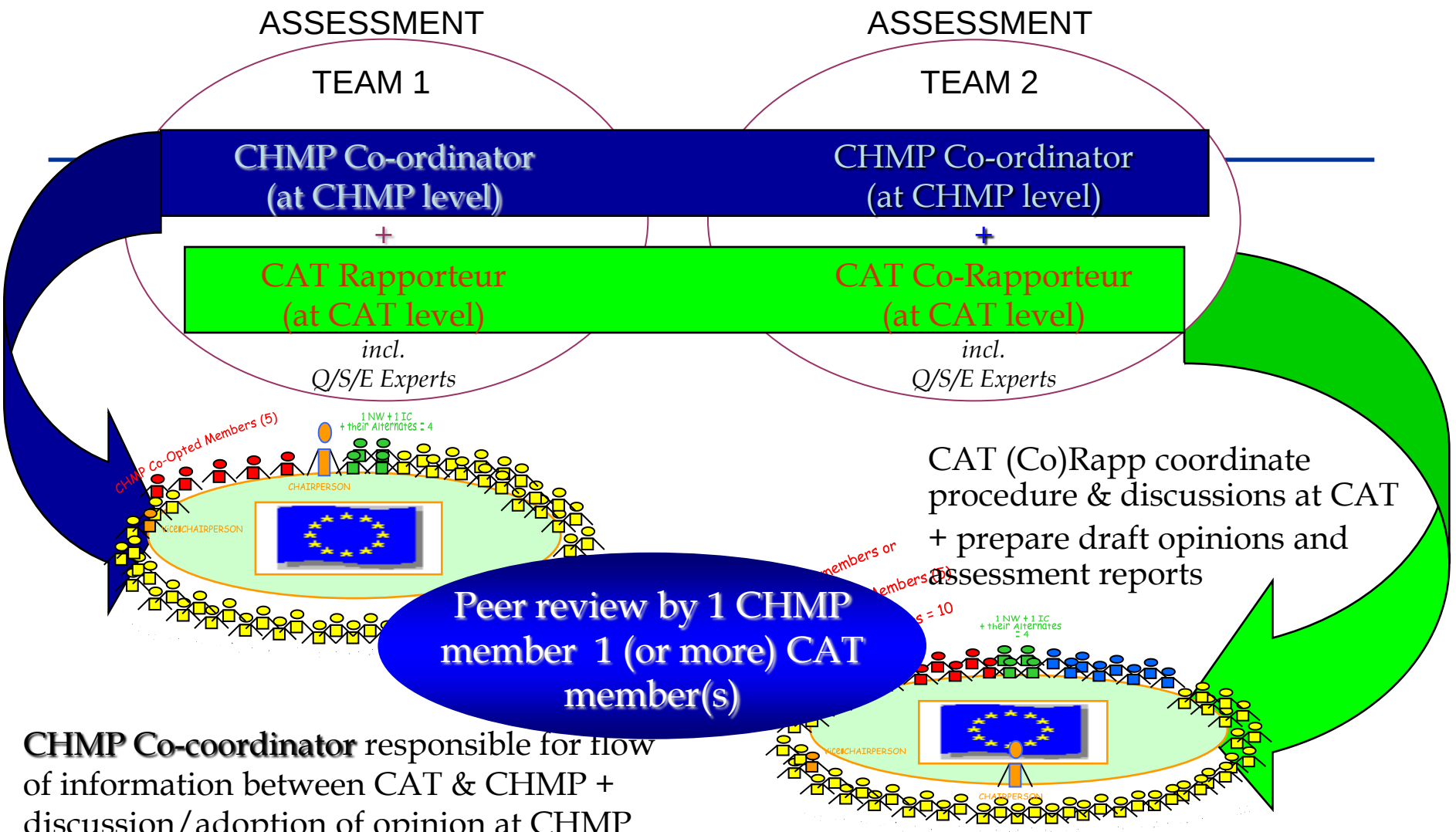
EU Marketing Authorisation (MA) for ATMPs

A medicinal product may only be placed on the market in the EU, when a **marketing authorisation** has been issued by the EU Commission
(via the Centralised Procedure – European Medicines Agency)

It may receive a national authorisation by the competent authority of a EU Member State (hospital exemption under art 28 of the Regulation 1394/2007)

Centralised Procedure results in Marketing Authorisation valid whole EU

- **Single application to EMA → one scientific evaluation**
- **Scientific Committee:** CAT + adoption by Committee for Medicinal Products for Human Use (CHMP)
- **Maximum legal time limit** 210 days evaluation → CAT Opinion → CHMP Opinion → EU Commission Decision
- **1 Trade name and 1 Labelling** (all EU languages identical)
  Summary of Product Characteristics
  User Package Leaflet
  Package Labelling



CHMP Co-coordinator responsible for flow of information between CAT & CHMP + discussion/adoption of opinion at CHMP

Role of CAT (Co) Rapporteur

- responsible for leading the scientific evaluation and the discussion at the CAT.
- to perform the scientific evaluation of ATMPs,
- to prepare AR, LoQ, joint AR and LoOI & circulate to CAT / CHMP members
- to identify the need for WP/SAG/Notified Bodies/Inspections involvement

Role of CHMP Coordinator

- ensure the flow of information to CHMP, presentation to CHMP and to guide the CHMP discussion at time of adoption of opinion.

- to provide input to all the relevant milestone documents (LoQs, LoOI, AR).
- to join the oral explanation at the CAT, if needed.
- to identify the need for WP/SAG/Notified Bodies/Inspections together with the Rapporteur.

EMA product team

Product Team Leader (PTL) Q or S/E
Product Team Member (PTM) Q or S/E
Regulatory Affairs
Inspection (GMP/GCP)
QRD/Medical information
Pharmacovigilance/RMP
Paediatric (if applicable)

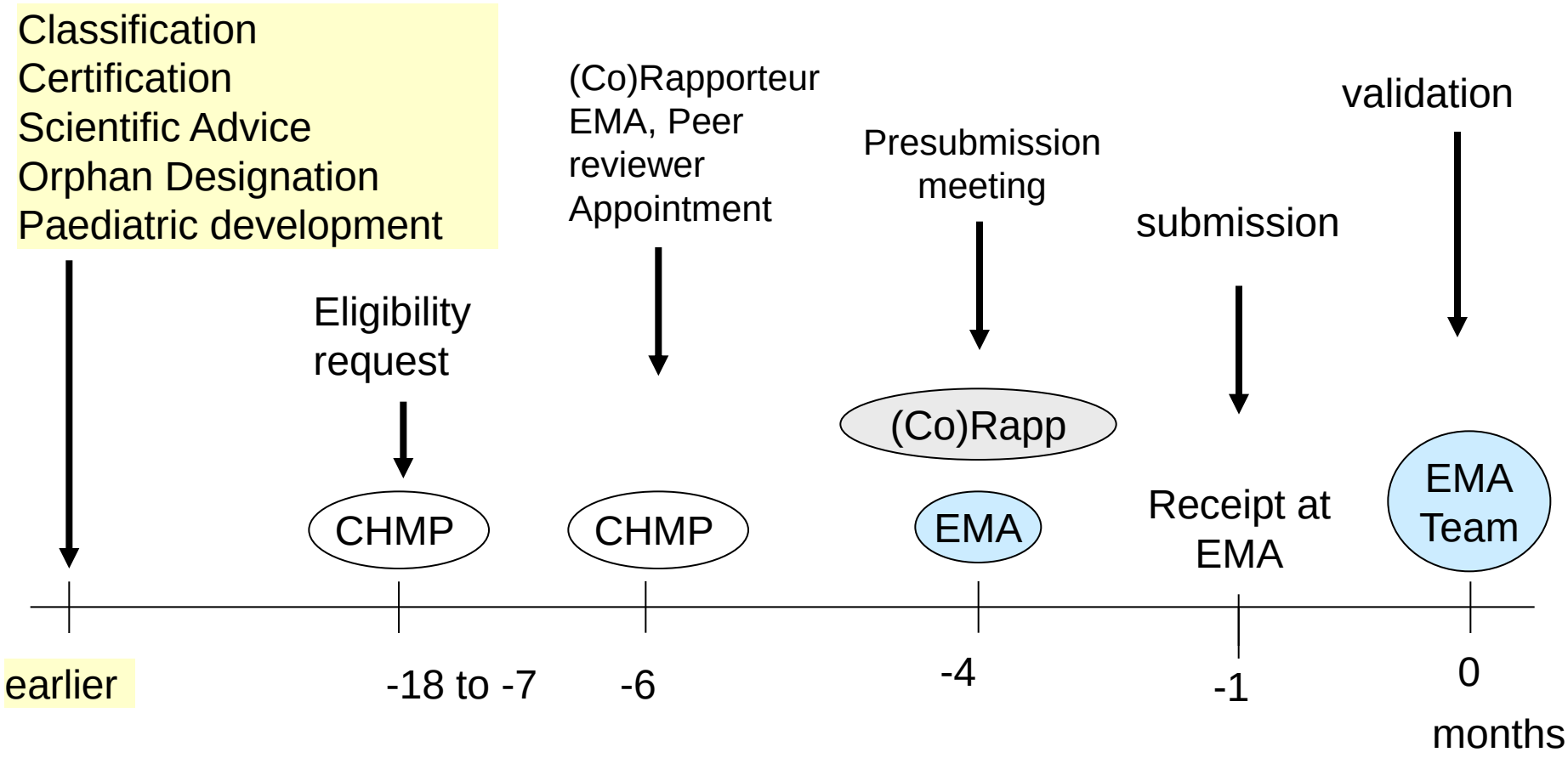
Role of EMA project team

- to act as a contact point between Applicant, EMA , (Co)Rapporteurs and Committees;
- to adhere to legal timeframe of 200 / 210 days (excluding clock-stops) for CAT/CHMP opinions.
- to ensure full transparency of the evaluation to CAT and CHMP
- to prepare the AR & opinion (on the basis of CAT's (Co)-Rapporteur(s)' AR) with scientific & regulatory consistency
- to communicate relevant public information on outcome of assessment of ATMPs.

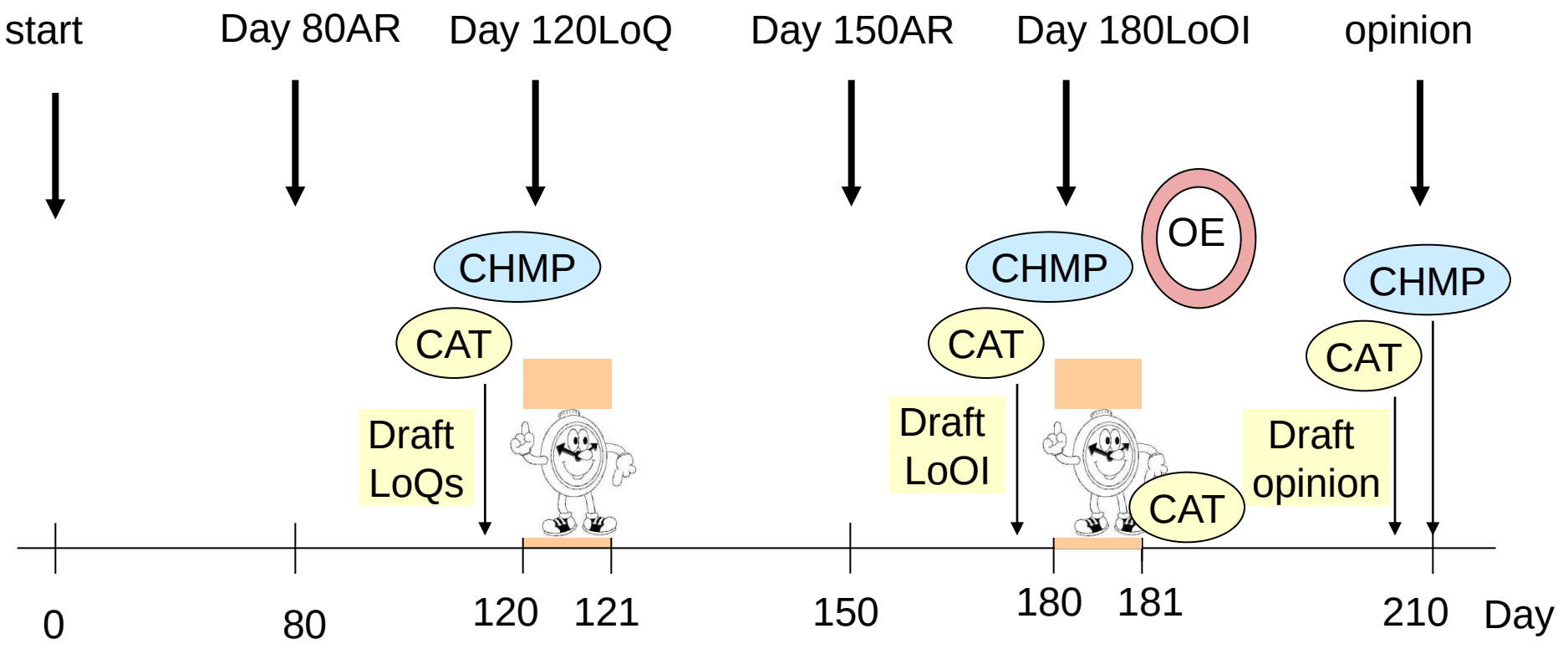
Procedure for initial MA review

Initial MAA procedure

pre-submission activities



Initial MAA procedure



Role of the CAT

- adopt Day 120 LoQs, Day 170 LoOIs and the draft opinion.
- the oral explanation takes place in front of the CAT.
- agree on the need to involve WP, SAG, Notified Bodies consultation/Inspections.

Role of the CHMP

- appoints Rapp and CoRapp evaluation teams.
- is informed during its plenary meetings of the key ATMPs scientific issues and/or divergences & can raise issues to the CAT/applicant
- adopts the final CHMP opinion.
- CHMP is responsible for the re-examination of the CHMP opinion

Role of the Peer reviewer

- to provide comments on the milestone documents
- to comment on the appropriateness of WP/SAG/Notified Bodies/Inspections consultation during the comment phase
- to follow the Oral Explanation in front of CAT, if necessary

Responsibilities of Rapporteur and Co-Rapporteur

• The role of the CAT Rapporteur and CAT Co-Rapporteur together with the appointed Assessment Team members is/are **to perform the scientific evaluation of ATMPs, to prepare an assessment report and to circulate it to the CAT and CHMP members according to the timetable agreed** for the evaluation procedure and taking into account the timeframe laid down in the relevant legislation

• For the evaluation of new marketing authorisations, Type II variation applications involving a new indication and renewals, the **Rapporteur is supported by the Co-Rapporteur**

Pre-evaluation

•presubmission meeting between the Applicant, EMA and (Co) Rapporteur teams (usually via separate meetings). The **purpose of this meeting is to discuss the proposed contents of the application**, so that the Rapporteur, Co-Rapporteur and the EMA can be introduced to the file. EMA/Rapp teams may provide comments relating to completeness of the submission, but Applicant decides when to file. It is not the purpose of these meetings to offer scientific advice to the Applicant.

• In between the start of the centralised procedure and D120, both teams should refrain from contacting the Applicant to facilitate the review of the dossier

Primary evaluation

- dossier (modules 3 / 4 / 5, RMP, ERA) evaluated by both assessment teams and the corresponding assessment reports together with an overview are circulated on day 80 at latest. **Rapporteur/Co-Rapporteur is responsible for the quality of all documents and for circulation of the documents within the agreed timeframe**

- both teams report whether inspections (GMP, GLP, GCP, PhV) are considered necessary

- main task for the Rapporteur and Co-Rapporteur is to define the **benefit/risk profile** for the product in the applied indication. B/R assessment should be based on all information gathered from different sections (Q/NC/C/RMP)

Building up the B/R profile

CMC: Suitability of starting/raw materials and manufacturing processes, consistency of production, quality of the DS and DP, validity of analytical procedures, release specifications (DS/DP), comparability of commercial and (pre)clinical batches, stability, GMP compliance

NC: Proof-of-concept, PD and PK studies, toxicological studies, availability and suitability of animal models, ERA, GLP compliance

C: PD, PK, mode of action, dose-finding, safety, efficacy, RMP, validity of pivotal results (study designs, number of patients, end-points, comparator, statistical methods), wide human exposure, GCP and PhV compliance

Additional: quality of the dossier, compliance with guidelines, scientific advice

Evaluation of Applicant´s responses

• both teams take part to evaluation of Applicant´s responses. Usually responses to major objections are assessed by both teams; other concerns assessed by the team that has raised the question. Questions raised by CAT/CHMP members assessed by the Rapporteur

• Rapporteur / Co-Rapporteur teams together draft a D150 JAR (D180 JAR) and D180 List of Outstanding Issues (LoOI) for further discussion in CAT and CHMP; **B/R profile re-evaluated**

• need for oral explanation proposed by (Co)-Rapporteurs and determined by the CAT

D180 - D210

Rapporteurs responsible for

- debriefing of the Applicant after D120 and D180
- evaluation of Applicant´s responses to LoOI
- drafting the final AR and opinion for CAT/CHMP discussion
- evaluation and approval of product information (SPC, PIL, labelling)
- EPAR (European public assessment report)

Challengies to consider?

- ***Short shelf-life***
- ***Autologous product***
- ***Difficulties to find a suitable potency test***
- ***No suitable animal models***
- ***Wide clinical experience already***
- ***Administration of the cells impacts the final outcome / rare diseases / unmet medical need / proper comparator not available / Blinding not possible***

Meetings with the Applicant, SAG and other stakeholders

- Whenever meetings between CAT Rapporteur or CAT Co-Rapporteur with Applicants or Marketing Authorisation Holders take place, **minutes of all contacts shall be made available to all the Assessment Team members and to the EMA Secretariat**

- Scientific Advisory Group meetings can be arranged when supported by CAT; Rapporteur and Co-Rapporteur take part to the discussions

- Rapporteur and Co-Rapporteur may establish contacts on an advisory basis, with representatives of patient organisations and health-care professionals' associations relevant to the indication of the medicinal product concerned

Role of inspectors during a MAA

• if (Co)Rapporteurs identify a need for inspections (GMP, GLP, GCP, PhV) and the request is supported by CAT and CHMP, EMA Inspector´s sector will co-ordinate the conduct of the inspection(s)

• inspectorate from the ”supervisory” member state will provide the lead inspector; inspectors and/or assessors from the Rapporteur/ Co-Rapporteur teams/agencies may join the inspection when requested

• inspections should be conducted to verify compliance with legal requirements (GMP: 2003/94/EC; GLP:2004/9/EC, 2004/10/EC; GCP:2001/20/EC)

• inspections should be carried out within the 210 days, preliminary report before D180 to allow discussion of the findings before final LoOI

Legislation and guidance

- Regulation 726/2004/EC, Directive 2001/83/EC, Regulation 1394/2007/EC, Notice to Applicants vol. 2A

- assesment templates and D80 AR guidance

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000121.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580022719&jsenabled=true

- procedural guidelines for centralised MAA

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000168.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac0580027256#section3

- CAT rules of procedure, EMEA code of conduct

Thanks for your attention